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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/823,847 | 03/30/2001 | Peter J. Sims | 26336-23 | 7002 |

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BENESCH, FRIEDLANDER, COPLAN & ARONOFF LLP
ATTN: IP DEPARTMENT DOCKET CLERK
2300 BP TOWER
200 PUBLIC SQUARE
CLEVELAND, OH 44114

| EXAMINER |
|---|
| FOLEY, SHANON A |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

DATE MAILED: 06/18/2002 12

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/823,847 | SIMS ET AL. | |
| | Examiner | Art Unit | |
| | Shanon Foley | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *1-25 and 35-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of group 25 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that the Office has not restricted the inventions under the proper type, i.e., 37 C.F.R. § 1.142 as opposed to the restriction as it relates to different species under 37 C.F.R. § 1.146. Applicant also states that assuming the Office is correct in determination of independent inventions, the application has presented a reasonable number of sequences to search and this reasonable number of nucleotide sequences has been partly waived by the Commissioner. Applicant concludes that an undue search requirement is not required for the present application.

Applicant's arguments have been fully considered, but are not found persuasive because the restriction in the instant case is drawn to independent and distinct inventions, not species. The invention that applicant elected is drawn to a method which uses a Phospholipid Scramblase polypeptide that has the amino acid of SEQ ID NO: 2 and fragments thereof. The specific sequence and fragment sequences thereof are all under consideration for the elected group. The claims of group 25 do not recite other sequences for use in the method. Therefore, arguments drawn to election of species are moot with the election of this group. However, with respect to other independent inventions that are drawn to distinct sequences, all of the nucleic acid and polypeptide sequences claimed are unrelated to one another in structure and function and are therefore, not species of one another, but are patentably distinct entities. Each sequence comprises completely different physical properties, such as chemical structure, primary

sequence, evidenced by the different SEQ ID NO. assigned to each, and molecular weight. Therefore, each invention is non-obvious over each other.

Furthermore, the elected group does not encompass using nucleic acids in the method, so the reasonable number of nucleic acid molecules waived by the Commissioner does not apply. Even so, it has been determined that each nucleic acid sequence in other non-elected groups are patentably distinct and a search for more than one of the specific and distinct sequences would pose an undue search burden for the Office. A divergent and non-overlapping search burden is required by the Office because of the structural uniqueness of each sequence. Each SEQ ID NO. must be searched independently of all others in the patent and non-patent literature databases world-wide, which uses the time and resources of the Office as there are only two sequence processors for the entire technology center. This sequence search does not preclude a worldwide patent search under the appropriate classes and subclasses and cross-referencing indexes and a non-patent literature search for relevant terms. Further, each of the inventions are classified separately, which is another indication that a burdensome search would be required for each of the patentably distinct inventions.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-25 and 35-58 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11. Claims 26-34 are under consideration.

***Sequence Compliance***

The specification is objected to for failing to adhere to the requirements of the sequence rules. Applicant must append SEQ ID Nos. to all mentions of specific sequences in the specification. See 37 CFR § 1.821(d). Examples in the specification that lack appropriate sequence identifiers are found in the middle of page 7, pages 50-52, Table 1 on page 56, and the last paragraph on page 61. The examples listed may not be exhaustive of all of the sequences missing the required SEQ ID NO. Applicant is required to append a SEQ IDNO. to each sequence in the disclosure.

***Specification***

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see example 11 on page 54. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29, 30, and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 is drawn to an infection of a "membrane-bound" virus. It cannot be determined whether the viral infection only encompasses viruses presently attached to a membrane or whether the infection involves viruses whose mode of transmission is by binding to a membrane.

Claim 30 recites the limitation "polypeptides" (emphasis added) in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 34 is drawn to the fragments of Phospholipid Scramblase being peptidomemetics. It cannot be determined whether the fragments are mimicking the enzyme structure or functional activity or whether the fragments in the claim are mimicking the Phospholipid Scramblase polypeptide, any possible fragment of the enzyme, or the PPxY sequence motif.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a method of inhibiting or preventing any known and unknown viral infection by introducing a Phospholipid Scramblase polypeptide or any fragment thereof containing an amino acid sequence PPxY. The instant disclosure does not teach a fragment of Phospholipid Scramblase that only contains this motif that is capable of the required inhibitory function. The disclosure also does not teach all of the possible fragments of Phospholipid Scramblase that contain this motif that are capable of the inhibition of any virus. Nor is there any teaching in the instant specification that would indicate that every possible fragment of Phospholipid Scramblase would bind every protein at every WW sequence motif comprised within a targeted protein. Also, as discussed above, it cannot be determined whether the

fragments of claim 34 are mimicking the structure or function of Phospholipid Scramblase or any of the possible fragments containing the PPxY motif, or whether the peptide mimics are imitating the structure or function of this motif. Therefore, since the disclosure lacks a teaching for any of the species within the genus of fragments and does not teach how the skilled artisan could identify any possible fragment of Phospholipid Scramblase with the required sequence motif that retains the required activity, it is determined that the specification does not convey possession of the species within the genus claimed.

Claims 26-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of inhibiting or preventing infection of any virus, known and unknown, by introducing Phospholipid Scramblase or any fragment containing the sequence PPxY into cells. Therefore, the claims encompass preventing and inhibiting viral infections of yet-undiscovered viruses. The claims also encompass preventing viral infection in known viruses such as Ebola, Marburg, and HIV, with no art-recognized animal model. See the reviews of Wilson et al. (Cellular and Molecular Life Sciences. 2001; 58 (12-13): 1826-41) and Klein et al. (Clinical Therapeutics. 2000; 22 (3): 295-314) for general teaching in the art for HIV and Ebola vaccines. The specification does not teach an appropriate animal model for these viruses or use an animal model for other viruses to be inhibited.

The instant disclosure fails to describe every possible fragment of Phospholipid Scramblase containing the PPxY sequence that retains the required function and fails to teach

how one skilled in the art could recognize any fragment containing this motif that would be able to inhibit and prevent any known and unknown viral infection. The disclosure also fails to teach effective delivery of Phospholipid Scramblase, fragments, and/or memetics to bind every protein containing the targeted WW sequence motif. The skilled artisan would be concerned about delivering such an enzyme or fragments thereof to cells because Phospholipid Scramblase function has not been clearly defined, see Sims et al. (Thrombosis and Haemostasis. 2001; 86 (1): 266-275, abstract only).

There is also no teaching in the specification that addresses concerns in the art for effective delivery while not interrupting normal cellular function. There is no way to determine how the instant enzyme, delivered in such large quantities in order to bind every protein comprising a WW motif would effect the host. This concern is also admitted in the specification at the top of page 64. There are no working examples for inhibiting every type of viral infection and there is no data presented in the instant specification that would indicate to the skilled artisan that the claimed enzyme and/or fragments and/or memetics thereof would be able to inhibit or prevent any known and yet-to-be discovered virus.

The skilled artisan would also doubt the efficacy of the claimed enzyme and any fragment thereof to inhibit or prevent any viral infection because other factors involved in viral infection are not addressed in the disclosure. In addition, the function of Phospholipid Scramblase is admittedly speculative; see the first paragraph on page 3 page 12, paragraph 50, and page 63, paragraph 177 of the specification. Therefore, the skilled artisan would be unable to structurally or functionally identify an effective fragment, peptidomemetic or Phospholipid Scramblase enzyme of the claimed invention.

Moreover, the consensus sequence, PPxY, is only implicated in the virus budding process of rhabdovirus, filoviruses, and retroviruses, and only where the motif is present in the viral matrix proteins, see paragraph 53 on page 13. There is no indication that the motif that may be coincidentally present in other viruses is also implicated in the budding process.

Example 2 on page 43 indicates that the transcriptional control of a specific Phospholipid Scramblase, PLSCR1, is regulated by a single INF-responsive element in vitro in select cell lines. There is no data for other phospholipid scramblases or data in non-recombinant cell lines.

Example 4 on pages 45-46 is drawn to studying antiviral function of PSCR1 on rhabdovirus, VSV. INF inhibits VSV replication at a late stage and the inventors teach that the M protein contains the PPxY motif. It cannot be determined whether the inhibition of VSV is a result of PSCR1 or the addition of interferon in the example because there is no data for quantitative measurement of INF produced as a result of overexpression of PLSCR1. There is also no data for PLCR1-negatively expressing cells treated with the addition of INF in correlative amounts that may have been induced by the expression of PLCR1. Also, the example teaches that "virus yield was suppressed 2.5 fold in PLSCR1-expressing cells compared to empty vector cells." This data does not indicate inhibition or prevention of viral infectivity.

In addition, the inventors admit on page 63, paragraph 177 that the presumed activity of phospholipid scramblase on cell membranes cannot be predicted by level of enzyme expression, but that other factors are involved. There is no teaching or indication that would enable one skilled in the art consider these other unknown factors alluded to. Nor would the skilled artisan be able to predict the effect of the enzyme merely by accomplishing its expression in a recombinant cell in vitro.

Therefore, due to the scope of the claims encompassing every phospholipid scramblase and any fragment or mimetic structurally or functionally derived therefrom, the lack of predictability by the skilled artisan to make or recognize a fragment of phospholipid scramblase with a required function that is little understood, the nature of the invention drawn to inhibiting and preventing any known and unknown viral infection, the state of the vaccine art for preventing the claimed viruses, the lack of defined function for phospholipid scramblase in the art, the lack of working examples demonstrating viral inhibition and/or prevention with phospholipid scramblase, the lack of teaching for how to administer or practice the claimed method, the lack of predictability for in vivo effect by administering the claimed enzyme, it is determined that undue experimentation would be required of the skilled artisan to make and use the invention.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley/SAF
June 9, 2002

JAMES HOUSEL 6/17/02
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600